

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Alan P. Kozikowski *et al.*

Application No.: 10/614,498

Confirmation No.: 8108

Filed: July 7, 2003

Art Unit: 1625

For: HISTONE DEACETYLASE INHIBITORS AND
METHODS OF USE THEREOF

Examiner: R. J. Desai

PRE-APPEAL REQUEST FOR REVIEW

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sirs:

Responsive to the Final Office Action mailed on October 27, 2008 ("Final Office Action"), the period for reply having been extended to April 27, 2009, by the payment of the fee for a three month extension of time herewith, and in conjunction with a Notice of Appeal under 37 C.F.R. § 41.31 and appeal fee payment, Applicants respectfully request a pre-appeal brief review of the above referenced application.

I. Status of the Claims

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81 and 90-93 are pending. Claims 1-5 and 32 stand rejected, and claims 6-8, 92 and 93 are allowed. Claims 41, 50, 60-62, 64, 73-8, 90 and 91 have been withdrawn from consideration and claims 9-31, 33-40, 42-49, 52-59, 65-72 and 82-89 have previously been canceled.

II. Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-5 and 32 as being allegedly obvious over Richon et al. Proc. Natl. Acad. Sci. Vol. 95, pp. 3003-7 (1998) ("Richon") and WO0226696 to Watkins et al. ("Watkins"). *Final Office Action* at p. 2-3, 6-10 and 14-16. Applicants respectfully traverse this rejection because the Final Office Action fails to establish a *prima facie* case of obviousness.

The Examiner points to Richon's disclosure of 3-Cl-UCHA (compound 7 of Richon), and contends that "the difference is only that of m being a zero instead of 1." *Final Office Action* at p. 8. The Examiner states that Watkins describes trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), as well as several other hydroxamic acid-containing compounds. The Examiner further states that "Watkins refers to the Richon and Jung et al. 1997, 1999," and that Jung et al "teaches that there is a binding region and enzyme inhibiting group is sep[arated] by a spacer. A variety of spacers are disclosed." *Id.* at p. 8-9. Based on these teachings, the Examiner concludes that "the link of the phenyl ring can be attached to the N of the urea or to a carbon atom and it would still retain its properties . . . In other words knowledge of the prior art compounds would have motivated one of skill in the art to modify the chain from m=0 to m=1 to 4, CH₂ linkage to obtain the compound of the instant invention. *Id.*

As explained in Applicants response filed on July 31, 2008 ("July 31, 2008, Response"), the Federal Circuit has recently clarified the application of the Supreme Court's *KSR* decision (127 S.Ct. 1727 (2007)) to chemical compound claims. In *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* Slip Op. 2007-1397 (Fed. Cir. July 21, 2008), the court stated that in order to establish that claimed compound is obvious over a structurally similar compound, there must be: (1) a starting reference point in the art, (2) reasons for one skilled in the art to make modifications, and (3) reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions." *Id.* at p. 8. There must be "some motivation that would have led one of ordinary skill in the art to select and modify a known compound (i.e. a lead compound)." *Id.* (emphasis added); *see also Takeda v. Ranbaxy*, 492 F.3d 1350, 1361 (2007).

Applicants have previously argued that the Examiner has failed to provide a reasoned identification of a lead compound. *July 31, 2008, Response* at p. 10. Richon describes 7 hybrid polar compounds ("HPC's") that inhibit HDAC. *Richon* at abstract. Of these seven compounds, the Examiner has selected 3-Cl-UCHA. The Examiner points to rationale for selecting this specific compound as a lead for modification, but rather, appears to use Applicants own disclosure as a blueprint. Richon describes several different assays for comparison of the seven described compounds, and does not even test 3-Cl-UCHA in all of these assays, nor does Richon provide any reasons for selecting 3-Cl-UCHA. In fact, Richon examples that increasing rigidity in the spacer, as in CBHA, and adding another hydroxamic acid group, as in SBHA, increasing activity. Despite these teachings, the Examiner selects a compound containing neither of these features.

The Examiner also states that “Watkins refers to the Richon and Jung et al 1997, 1999,” but fails to explain the significance of this referral. In fact, Watkins cites Richon and Jung amongst a laundry list of other references spanning eight pages, which describes a myriad of different HDAC inhibitors. *Watkins* at pp. 5-12. Watkins does not point to Richon as describing a desirable lead compounds, much less 3-Cl-UCHA in particular. Moreover, Watkins describes 152 compounds, yet the Examiner has selected for comparison, out of all of the possible variations in structure, compounds 41, 6, 35, 36, and 37. *Final Office Action* at p. 15. The only rationale for selecting these particular compounds could be Applicants’ own disclosure.

In addition to failing to adequately identify a lead compound, the compound the Examiner also has failed to provide any rational to make modifications to the compound, let alone the proposed modifications that the Examiner suggests. *July 31, 2008, Response* at p 11.

Finally, the Examiner states the “[i]n the absence of a showing of unexpected results just changing the linker by one CH₂ is considered prima facie obvious.” *Final Office Action* at p. 2. Applicants note that although homology “must be considered with all other relevant facts in determining the issue of obviousness,” it “should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed as a whole.” M.P.E.P. § 2144.09. As explained above, the cited referenced describe a variety of different compounds, and the Examiner has failed to provide a reasoned identification of a lead compound for modification such that the skilled artisan would arrive at the presently claimed compounds.

For at least the reasons set forth above and all of the reasons of records, Applicants submit that the present claims are not obvious over Richon and Watkins.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintains the rejection of claims 1, 3, 4, and 32 because the specification allegedly fails to enable these claims. The Examiner stresses in particular, compounds where R¹ is a heterocyclic group. *Final Office Action* at pp. 3-6, 10-13, 16-18. Applicants respectfully traverse.

As an initial matter, the Examiner now contends that she “finds it even more unconvincing as the applicants argue that modification of a CH₂ linkage is not obvious, whereas any heterocyclic group for R₁ would have the same activity.” *Final Office Action* at p. 4. Applicants submit that the arguments of record that the present claims are enabled by *Applicants own specification* are irrelevant to the non-obviousness of the present claims over Richon and Watkins.

Applicants have explained in the record that the present claims are more than sufficiently enabled under *In re Wands*, 858 F.2d at 737; M.P.E.P. 2164.01(a). Specifically, Applicants have addressed the breadth of the claims (*July 31, 2008, Response* at p. 12), The nature of the invention (*Id.* at p. 12-13), the state of the prior art (*Id.* at p. 13-15), the level of ordinary skill (*Id.* at p. 15), the amount of guidance provided by the inventor (*Id.* at p. 15), and the existence of working examples and the quantity of experimentation needed to make and use the invention (*Id.* at p. 16). The Examiner's *Wands* analysis can be found at pages 16-17 of the Final Office Action.

Nevertheless, the Examiner insists that "Applicants compounds are drawn to treating cancer which is a highly unpredictable art." *Id.* at p. 4. The Examiner further stresses difference between *in vivo* and *in vitro* assays. *Id.* In particular, the Examiner contends that the state of the prior art involves screening *in vitro* and *in vivo*, and there is absolutely no predictability and no established correlation between different substitutions on a core that they would all behave in the exact same way." *Final Office Action* at p. 17 (emphasis added). The Examiner further contends that the pharmaceutical art is unpredictable, "requiring each embodiment to be individually assessed for physiological activity." *Id.* (emphasis added). The Examiner thus appears to expect Applicants to describes each species and test it *in vivo* in order to be entitled to claim the present genus.

Applicants have repeatedly explained in the record that this is an incorrect standard. Absolute predictability is not required, nor must every species be made tested, nor must each species behave "in the exact same way." *July 31, 2008, Response* at p. 12-13. Moreover, Applicants have explained in the record that even the courts and the Board have recognized advanced in the art with respect to cancer treatment. *July 31, 2008, Response* at p. 14-15. For example, *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995), the Federal Circuit recognized that *in vitro* tumor models were sufficiently enabling, even for method of treatment claims.

The Examiner also has stated that "[t]he instant specification does not have any working examples no any invitro[sic] or invivo[sic] data that they do have any activity." *Final Office Action* at p. 17. As Applicants have explained in the record, this is a clear factual error. The specification discloses several examples and tests their activity for HDAC inhibition, cytotoxicity and radiation clonogenic survival data in Tables 3 and 4. *July 31, 2008, Response* at p. 16.

The Examiner now relies on *In re Fouché* 169 U.S.P.Q. 429 for the proposition that preparation of a compound having a heterocycle is required in order enable the present claims. *Final Office Action* at p. 5. Applicants submit that *Fouché* does not provide a blanket rule that a heterocycle example is required. Rather, *Fouché* merely requires that "an applicant must use *some*

technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim.” In the present application, the skilled artisan would readily understand that the synthetic schemes described at page 31 of the specification would be readily applicable to heterocyclic compounds. This teaching in conjunction with the working examples 1-8 meet the standard set forth by *Fouche*.

The Examiner additionally now states that “the term ‘substituted’ without modification or restriction . . . embraces millions of compounds.” *Final Office Action* at p. 5. This represents another factual error. The present claims do use the term “substituted” without modification. Instead, claim 1 recites that R¹ may be substituted with “one or more of the following groups: -halo, -C₁-C₆ alkyl, -O-C₁-C₆ alkyl, -OH, -CN, -COOR’, -OC(O)R’, NHR’, H(R’)₂, -NHC(O)R’ or – C(O)NHR’.” Applicants submit that the specification provides ample support for the presently claimed genus, as explained in the preceding paragraph.

IV. Conclusion

In light of the reasons forth above and of record in the application, Applicants respectfully submit that the pending claims are in condition for allowance. Applicants representative may be reached by telephone at 617-832-1223. Please grant any extension of time required to enter this amendment and response, and charge any additional fees to **Deposit Account No. 06-1448, GUX-012.01**

Dated: April 27, 2009

Respectfully submitted,

/Hilary Dorr Lang/

Hilary Dorr Lang

Registration No.: 51,917

FOLEY HOAG LLP

155 Seaport Blvd

Boston, Massachusetts 02210

(617) 832-1223

Attorney for Applicants